Attorney Docket No. TSR-10002/38

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BOARD OF APPEALS AND INTERFERENCES

Applicant:	Hilfinger, J, et al.	
Serial No.:	10/706,738	Group Art Unit: 1635
Filed:	November 12, 2003	Examiner: Richard Schnizer
For:	METHODS AND COMPOSITIONS OF GENE DELIVERY AGENTS FOR SYSTEMIC AND LOCAL THERAPY	

APPELLANTS' REPLY BRIEF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

A s required under § 37 C.F.R. 41.41, this reply brief is filed within two months of the Examiner's Answer.

RESPONSE TO EXAMINER'S ARGUMENTS

The Examiner's Position

Examiner based the rejection of claims 8-10, 13, 14, 19, 20, 22, 24, 26, 27, and 30 as obvious under 35 U.S.C. § 103(a) over Niedzinski, in view of Keener, and Gebeyehu.

Niedzinski is cited as teaching "cholic acid conjugates comprising a polyamine DNA binding domain, their use to protect DNA from degradation in the gastric system, and their use to deliver plasmids to NIH 3T3 cells in vitro." (Paper No. 20070907, pg. 3.) The Examiner in an Office communication dated September 17, 2007 states that: "It would have been obvious to one

of skill in the art at the time of the invention to substitute any hydrophobic bile acid or cholesterol derivative for the cholic acid of Niedzinski." (Paper No. 20070907, pg. 4).

Keener is cited as teaching "the use of bile acids, and cholesterol derivatives generally, as hydrophobic conjugates to aid in the cellular entry of a conjugated peptide." (Paper No. 20070907, pg. 3.) Examiner bridges Niedzinski with Keener because "Niedzinski considered his conjugation technique to be applicable to a variety of bile acids (see last sentence of column 1 on page 724), and it was clear that it could be applied to either the C3 hydroxyl (sic), so the presence of a carboxyl group was not required." (Paper No. 20070907, pg. 3) (emphasis added).

Gebeyehu is cited as teaching reagents and methods for intracellular delivery of nucleic acids that are cationic lipids with the formula ABZ where the A represents a steroid such as cholic acid, stigmasterol, or ergosterol, B represents a linker, and Z may be a nucleic acid binding domain such as a polyamine or polycationic peptide. (Paper No. 20070907, pg. 4.) Examiner's position is that "[i]t would have been obvious to one of ordinary skill in the art at the time of the invention to substitute a nucleic acid binding peptide [of Gebeyehu] for the nucleic acid binding polyamine of Niedzinski because these nucleic acid binding moieties were recognized in the art as equivalents. (Id. at 5.) Gebeyehu is further referred on page 11 of Paper No. 20070907:

> Regarding Gebeyehu, Applicant argues that the reference does not teach or suggest the use of any cholesterol derivative other than stigmasterol, ergosterol, or cholic acid. Gebeyehu was not relied upon to teach any derivative other than these. The cholesterol derivatives are taught by Niedzinski and Keener. Gebeyehu taught the use of nucleic acid binding domains, such as a polyamine or a polycationic peptide, in combination with a steroid such as cholic acid, stigmasterol, or ergosterol, and a linker. Clearly polyamines and cationic peptides were recognized in the art as equivalents as DNA binding domains in delivery compositions, such that it would have been obvious to substitute one for the other in the invention of Niedzinski as modified by Keener.

Thus, Gebeyehu is cited merely for the proposition that polyamines and cationic peptides are art recognized equivalents. (*see also* Paper No. 20070907, pg. 5.)

Examiner based the rejection of claims 15 and 16 as obvious under 35 U.S.C. § 103(a) over Niedzinski, in view of Keener, and Gebeyehu, in further view of Perrie. The base references are cited as lacking any teaching of protein secretion from target cells or claiming the composition as a therapeutic compound. (Paper No. 20070907, pg. 6.) Perrie is cited as teaching "oral intragastric delivery of cationic liposome comprising nucleic acids encoding the S (small) region of the hepatitis B surface antigen (HBsAg) . . . [wherein] . . . DNA vaccines encoding HBsAg were formulated with cationic lipids (DOTAP) and administered orally." (Paper No. 20070907, pg. 6.) Examiner believes Niedzinski taught "that the lipid could be substituted for, or added to, such cationic lipids as DOTAP," and the Niedzinski compounds are art recognized equivalents of cationic lipids. (Paper No. 20070907, pg. 7.) Claims 15 and 16 are present in the rejection because of Examiner's belief that the nucleic acid of Perrie is a therapeutic product because it is "antibiotic in nature" such that it induces "an immune response against hepatitis B virus." (Paper No. 20070907, pg. 7.)

Examiner based his rejection of claims 11, 12, 15, and 16 as obvious under 35 U.S.C. § 103(a) over Niedzinski, in view of Keener, and Gebeyehu, in further view of Kitadai. The base references are cited as not teaching secretion of an expressed protein or a composition comprising a therapeutic compound. Kitadai is cited as teaching an expression vector encoding the secreted protein interleukin-8 that was transfected into cells using the cationic lipid LIPOFECTIN (DOTMA/DOPE). (Paper No. 20070907, pg. 8.)

Appellant's Position

A. **Rejection of Claims 8-10, 13, 14, 19, 20, 22, 24, 26, 27, and 30.**

No teaching in the cited prior art to combine Keener with Niedzinski and Gebeyehu as is required under Takeda and KSR.

In total, the arguments presented in Examiner's Answer suffer two major deficiencies. First, Examiner bridges Niedzinski with Keener because "Niedzinski considered his conjugation technique to be applicable to a variety of bile acids (see last sentence of column 1 on page 724), and it was clear that it could be applied to either the C3 hydroxyl (sic), so the presence of a carboxyl group was not required." (Paper No. 20070907, pg. 3) (emphasis added). A person having ordinary skill in the art recognizes that Niedzinski merely teaches a chemical synthetic strategy that is applicable to multiple bile acid salts. Niedzinski does not provide any reasonable expectation of success for substituting other bile acids since only one product of the Niedzinski synthesis, C(3) functionalized cholic acid compound 5 does not hinder the ability of cationic lipids to deliver nucleic acid to cells *in vitro*. The opposite result is taught for C(3) functionalized cholic acid compound 6 of Niedzinski that "inhibits the activity of DMDHP as a transfection agent." (pg. 725, second column, center.) Thus, Niedzinski's chemical synthetic scheme does not predict biological function. Second, if the hydrophobic nature of the C(3) functionalized cholic acid molecules were all that were required for functionality, then there would have been no need for Niedzinski to use cationic lipids to successfully deliver nucleic acid to 3T3 cells, and any hydrophobic molecule alone would be sufficient. Since Niedzinski's cholate 6 was inhibitory and cholate 5 stimulatory as an additive to known transfection agents, the hydrophobic nature of the cholates does not predict whether they will assist or hinder

transfection. Thus, the arguments presented in Examiner's Answer are readily recognized by a person having ordinary skill in the art to not be scientifically sound.

As was recently articulated by the Federal Circuit, for a case of *prima facie* obviousness to be found for chemical matter, "[i]n addition to structural similarity between the compounds, a *prima facie* case of obviousness also requires a showing of 'adequate support in the prior art' for the change in structure." Takeda Chem. Indus., Ltd. v. Alphapharm Pty, LTD, 83 USPQ2d 1169, 1174 (Fed. Cir. 2007). The court further made expressly clear that "in order to find a prima facie case of unpatentability in such instances, a showing that the 'prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention' was also required." Id. (quoting In re Deuel, 51 F.3d 1552, 1558 (Fed. Cir. 1995) (internal references omitted). The court clarified that this test for chemical compounds is "consistent with the principles enunciated in KSR." Id. (citing KSR Int'l Co. v. Teleflex, Inc., 127 S. Ct. 1727 (2007).

The rejections of independent claims 8 and 20 fail to satisfy a *prima facie* case of obviousness as enunciated in Takeda and KSR.

More specifically, to address the first flaw in Examiner's Answer, a person having ordinary skill in either the chemical or biological arts readily recognizes that a method of chemical synthesis does not equate to a method of predicting biological function. Drug discovery is fraught with examples of chemical synthetic strategies producing less than 1 in 1000 compounds with the desired biological activity. Appellant recognizes why this simple truth is not accepted by Examiner. Examiner's Answer unfortunately misunderstands this argument as stating that "Niedzinski does not teach modification at positions other than C(3), so one of ordinary skill would have no expectation of success in using cholesterol derivatives modified at

positions other than C(3)." (Examiners Answer, page 14, first paragraph.) That is not the basis of the argument. Instead, Niedzinski does not teach biological function of C(3) functionalized cholic acid molecules, only that one of them, cholate 5, does not hinder nucleic acid delivery by other cationic molecules. Niedzinski does teach that C(3) positions "may be functionalized for conjugation without compromising recognition by the bile acid transport system," (pg. 722, first column, center (emphasis added)) and "the robust nature of the C(3)-*N*-acyl imidazole should make this synthetic strategy adaptable to the synthesis of a variety of C(3) bile conjugates." (pg. 724, first column, final sentence (emphasis added).) Finally, contradictory biological function of cholates 5 and 6 is taught by Niedzinski:

> DMDHP was selected for the transfection experiments based on the superior transfection activity exhibited by DMDHP. Additionally, this provides the opportunity to determine whether adding a cholic acid amphiphile to a commercially available transfection system would impart a beneficial or detrimental effect on overall transfection activity. Cholate 5 was more active than cholate 6 as a transfection additive in the lipid formulation examined (Fig. 5) . . . [whereas] cholate 6 inhibits the activity of DMDHP as a transfection agent." (pg. 725, second column, center (emphasis added) (internal citations omitted).)

From this overall summary of the whole of Niedzinski's teaching, a skilled artisan has no reasonable expectation that (1) the synthetic strategy will predict an ability of the product to deliver nucleic acid to cells, and (2) that C(3) functionalized cholates have the ability to deliver nucleic acid at all, let alone finding from Niedzinski's results that non-C(3) functionalized bile acids will have efficacy in delivery of nucleic acid to cells as demanded in the instant claims.

Examiner contends that the cholates of Niedzinski were targeted to bile salt receptors, which are efficient at taking up bile salts generally. Appellant recognizes that Niedzinski teaches that bile salt receptors are efficient at taking up physiologically constructed bile salts with high

efficiency. However, the rejections require an unsupported leap to suggest that Niedzinski teaches that all bile acids (naturally constructed or synthetic and as a portion of a larger complex) are similarly suitable as a transfection agent toward any cell. This assertion is not borne out by careful analysis of the teaching of Niedzinski.

Examiner's position relies on the sentence bridging pages 721 and 722 of Niedzinski that states: "The enterohepatic receptors in the ileum are responsible for circulating between 12-30 g of bile salts in a day, and the bile salts are readsorbed in the terminal ileum with recovery efficiencies of up to 95%." (internal citation omitted.) However, a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983). Examination of the cited sentence with those immedialy preceding and following demonstrate that Niedzinski taught that the cholic acids synthesized therein may supplement transfection agents. A complete view of Niedzinski teaches:

> [W]e prepared novel transfection lipids from cholic acid . . . We understand that these compounds would localize lipoplexes to the epithelium of the terminal ileum by taking advantage of the bile acid specificity for enterohepatic receptors. The enterohepatic receptors in the ileum are responsible for circulating between 12-30 g of bile salts in a day, and the bile salts are readsorbed in the terminal ileum with recovery efficiencies of up to 95%. C(3)-functionalized cholic acid derivatives have shown the ability to interact with molecular receptors in the ileum, aiding the delivery of molecules through the intestinal wall. (emphasis added)

Thus, Niedzinski is limited to teaching functions of C(3)-functionalized compounds taught therein, and do not extend to other hypothetical compounds not envisioned by the Niedzinski reference, and Examiner's assertion is based on an incomplete reading of the Niedzinski reference. The simple statement that bile acids are efficiently taken up by receptors in the ileum

does not teach or suggest to a person having ordinary skill in the art that any modified cholate will have efficacy for the delivery of nucleic acid to a target cell. This is true particularly in light of Niedzinski's teaching being explicitly limited to compounds disclosed in the reference itself. Niedzinski envisioned only specific compounds, not an entire family, and not the compounds in the instant claims.

Examiner's Answer claims that since Niedzinski taught that the C(3) position in cholic acid could be modified without loss of receptor binding, a person of ordinary skill in the art would have a reasonable expectation of success in substituting other bile acids for cholic acid in the invention of the Niedzinski. Neither Niedzinski nor the other prior art of record suggests that the claimed structures will possess the same level of receptor binding or transfection efficiency absent C(3) modification. Further, neither Niedzinski nor the other prior art of record teach or suggest cholestanol, coprostanol, glycocholic acid, chenodeoxycholic acid, desoxycholic acid, glycochenodeoxycholic acid, taurocholic acid, and taurochenodeoxycholic acid as a functional group. Moreover, the teaching of Niedzinski itself is contradictory. Functional experiments were performend on cholates 5 and 6 of Niedzinski. As demonstrated in Fig. 5, cholate 5 enhanced the ability of known transfection agents. However, cholate 6 was inhibitory. Since both cholate 5 and 6 are C(3) and C(24) functionalized cholic acid, a person having ordinary skill in the art would have no reasonable expectation of success in generating an agent useful for delivery of nucleic acid to cells. Thus, consistent with the principles enunciated in Takeda and KSR, no explicit motivation is present in Niedzinski or the other prior art of record, and a *prima facie* case of obviousness is not established.

To address more specifically the second major flaw of the reasoning presented in Examiner's Answer, much of Examiner's position depends on the mistaken belief that "bile acid and sterol moieties generally would serve as a good hydrophobic group for facilitating the transfer of a conjugated hydrophilic group across a cell membrane, even in the absence of enterohepatic receptors." (Examiner's Response, pg. 13, first paragraph.) Examiner's response claims that the simple hydrophobic nature of sterols and bile acids direct their function and then builds on this error to suggest that any hydrophobic molecule can serve to transfer nucleic acid across a cell membrane. To support this assertion, Examiner highlights FIG. 5 of Niedzinski which "shows that the cholic acid conjugates can improve transfection of 3T3 cells which are fibroblasts, not gastric cells, and so would not be expected to express the gastric enterohepatic receptors." Id. A person of ordinary skill in the art recognizes that the experiments highlighted in FIG. 5 of Niedzinski demonstrate transfer into 3T3 cells due to the presence of DMDHP and DOPE, not the cholic acid derivative. Moreover, similarly hydrophobic cholic acid molecules demonstrate opposite results in Niedzinski. These experiments do not illustrate functionality of the cholic acid derivative. They merely demonstrate to a person of ordinary skill that cholate 5 alone does not destroy the functionality of the other cationic lipids, whereas cholate 6 does. If the hydrophobic character of bile acids were alone sufficient to support transfection, even in a modified state, there would have been no need for Niedzinski to combine cholates with DMDHP and DOPE to demonstrate nucleic acid uptake, and both cholates 5 and 6 would have been stimulatory.

The results of FIG. 5 of Niedzinski further refute Examiner's belief that a person having ordinary skill in the art would be motivated to use any cholate merely because of its hydrophobic nature. Taken to its logical conclusion, Examiner's assertion indicates that any hydrophobic

molecule capable of binding a nucleic acid would be suitable as a transfection agent- they are not. Simply because a single cholate component of a transfection system stimulates uptake of nucleic acid in cells driven by DMDHP/DOPE were another similar cholate is inhibitory, does not suggest to a person of ordinary skill that the hydrophobic nature of the cholate is itself responsible for the outcome. Similarly, uptake mediated by DMDHP/DOPE being stimulated by the C(3) functionalized cholate 5 of Niedzinski does not mean that the uptake is due to the presence of the C(3) functionalized cholic acids themselves. Indeed, since cholate 6 was inhibitory, a person of ordinary skill in the art recognizes that the cholates of Niedzinski have no stand alone positive transfection activity and the efficacy of cholate 5 must be due to independent effects on the structure of the DMDHP/DOPE transfection agents.

To address additional substantial errors in the reasoning presented in Examiner's Answer, the Answer mistakenly states that "for the recited cholesterol derivatives 'cholestanol' and 'coprostanol', the only position available for modification is the C(3) hydroxyl. These compounds lack any other hydroxyl or carboxyl group, so they must be modified at the C(3)." (page 14, final two sentences.) However, neither the claims nor the specification suggest that precursors of the claimed compounds must be cholestanol or coprostanol which are subsequently modified, but merely that the A-R_1 group of the entire synthesized molecule must be one of the Markush group including cholestanol and coprostanol. An ordinary practitioner readily recognizes that by reducing the 4,5 double bond on cholesterol a product of either cholestanol or coprostanol may be produced with functional groups at carbon 4 and/or 5. Additionally, chemical modification of the C(20-27) alkyl chain may result in cholestanol or coprostanol linked to the claimed Q in the final claimed structure. Methods of chemical modification of either of these positions were known in the art at the time of filing. (see e.g. Blagbrough, IS et

al., Biochem Soc Trans, 2003; 31(2):397-406.) Thus, Examiner's characterization that cholestanol and coprostanol must be modified at C(3) is in error.

A stepwise analysis of Examiner's overall reasoning is provided in the paragraph bridging pages 15-16 of Examiner's Answer. Therein the Answer states:

> [I]t would have been obvious to one of ordinary skill in the art at the time of the invention to modify bile acids at either of positions 3 or 24 for several reasons: 1) Niedzinski taught modification at position 3; 2) Gebeyehu taught modification at position 24; Niedzinski taught that modification of cholic acid at either position 23 (is 3 meant?) or 24 did not affect uptake by receptors; and 4) even in the absence of receptors, one of ordinary skill could have reasonably expected nucleic acid uptake due to the hydrophobic character of the cationized bile salts or sterols.

In response, while Niedzinski and Gebeyehu taught modification at positions 3 and 24 respectively, these modifications were limited to cholic acid alone in Niedzinski and additionally stigmasterol and ergosterol in Gebeyehu. None of these molecules are members of the instantly claimed Markush group, and the teaching of Niedzinski and Gebeyehu do not represent the explicit suggestion of chemical modification of the molecules in the instant claims as required by the Federal Circuit in Takeda. These failings are not corrected by Niedzinski's teaching that modification at position 3 or 24 does not affect uptake by receptors. Niedzinski taught merely that adding cholic acid compound 5 to a commercially available transfection system was not detrimental to the transfection activity of the commercially available transfection system. The opposite result was found with Niedzinski's cholic acid compound 6. An ordinary practitioner recognizes that this does not teach or suggest that other bile acids will support transfection activity.

Further in response, an ordinary practitioner recognizes that more than hydrophobic character is required to induce nucleic acid uptake, for if hydrophobic character were alone sufficient there would have been no need for Niedzinski to combine a commercially available transfection system with cholic acid compound 5 to induce cellular transfection. Moreover, although cholic acid compound 6 of Niedzinski is similarly a hydrophobic molecule, Niedzinski teaches that "cholate 6 inhibits the activity of DMDHP as a transfection agent." (pg. 725, second column, center.) These contradictory results with different forms of the same cholate, cholic acid, demonstrate that a person having ordinary skill has no reasonable expectation of success in substituting the cholates of Gebeyehu. Even less expectation of success follows from the contradictory results of Niedzinski for substituting the cholates of the subject claims, none of which are taught by the cited prior art. The prior art cannot be modified or combined to reject claims as *prima facie* obvious unless there is a reasonable expectation of success. In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As is readily recognized by an ordinary practitioner, no reasonable expectation of success of provided by the cited prior art combination, and the four steps to obviousness cited in Examiner's Answer at pages 15-16 do not provide the requisite pathway for finding a *prima facie* case of obviousness under the Takeda and KSR standard for the chemical arts.

Finally, the cholesterol derivatives of Keener are not functional equivalents of the C(3)-functionalized cholic acid derivatives of Niedzinski nor of the compounds of the instant claims. The bile acids of Keener are not known material based on suitability for intended use as Niedzinski teaches that suitability for delivery of DNA to cells requires both a C(3)-functionalized group and co-administration with synthetic lipids. Examiner's Answer states that Niedzinski merely "exemplifies these." (pg. 17, second paragraph.) However, it is clear from

Examiner's Answer that neither Niedzinski, Gebeyehu, nor Keener provide any teaching or suggestion that the bile acids of Keener would function in the method of Niedzinski as is required under the standards enunciated in Takeda and KSR. Neidzinski "requires" C(3) functionalization because the only compound taught not to be detrimental to the transfection efficiency of the commercially available transfection agents is modified at C(3). (cholate 5; see Table 2 and Figs. 4 and 5.) No teaching of Niedzinski suggests that compounds 1 or 2, which are not modified at C(3), are similarly not detrimental, let alone are themselves positively functional as transfection agents. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on Applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. *In re Ruff*, 256 F.2d 590, 118 USPQ 340 (CCPA 1958). Thus, there is no explicit teaching in the cited prior art to combine Keener with Niedzinski and Gebeyehu as is required under Takeda and KSR.

B. The rejection of claims 15 and 16 under 35 U.S.C. §103(a)

Niedzinski in view of Keener and Gebeyehu, in further view of Perrie fails to establish a *prima facie* case of obviousness for all elements of the instantly claimed invention.

Perrie is cited in support of a rejection of claims 15 and 16 because "the nucleic acid of Perrie is considered to be a therapeutic product that is antibiotic in nature by virtue of its activity in inducing an immune response against hepatitis B virus." (Paper No. 20070907, pg. 7.) Mere suggestion that a nucleic acid may be used as a therapeutic product does not suggest the structure or function of the conjugating agents of the subject claims to one having ordinary skill in the art.

The antibiotic nature of Keener's compound is of no import to suggesting the conjugating agent of the instant claims in light of the shortcomings of Niedzinski and Gebeyehu. Appellant submits that claims 15 and 16 are allowable on the basis of dependency from an allowable base claim and incorporates in its entity the above remarks regarding Niedzinski in view of Keener and Gebeyehu in that, alone or in combination, they are deficient in rendering obvious the claimed invention.

As such, Niedzinski in view of Keener and Gebeyehu, in further view of Perrie fails to establish a *prima facie* case of obviousness for all elements of the instantly claimed invention.

C. The rejection of claims 11, 12, 15, and 16 under 35 U.S.C. §103(a)
No expectation of success is present in the cited prior art combination.

Examiner's Answer continues to erroneously conclude that C(3)- and C(24)-functionalized cholic acid can substitute for any cationic lipid such as the LIPOFECTIN reagent of Kitadai. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on Applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. *In re Ruff*, 256 F.2d 590, 118 USPQ 340 (CCPA 1958). Niedzinski does not teach or suggest that the compounds taught therein can substitute for DMDHP, DOPE, (as taught by Niedzinski) DOTAP, LIPOFECTIN (as taught by Kitadai), or any combination thereof because Niedzinski simply does not teach functional equivalency. Merely teaching that the presence of a single cholate may not be detrimental to a known transfection system does not teach that all cholates act as a transfection system themselves. This is further supported by the finding in Niedzinski that while "cholate 5 was more active than cholate 6 as a transfection additive in the lipid formulations

examined (Fig. 5) . . . cholate 6 inhibits the activity of DMDHP as a transfection agent." (pg. 725, second column, center.) Thus, a person of ordinary skill has no reason to assume that any other compound would be effective as a transfection agent alone given the contradictory teachings of Niedzinski. The prior art cannot be modified or combined to reject claims as *prima facie* obvious unless there is a reasonable expectation of success. In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The expectation of success is not present in the cited prior art combination.

In addition to the above remarks, Appellant submits that claims 11, 12, 15, and 16 are allowable on the basis of dependency from an allowable base claim and incorporates in its entity the above remarks regarding Niedzinski in view of Keener and Gebeyehu in that, alone or in combination, they are deficient in rendering obvious the claimed invention.

Conclusion

In summary, Examiner's references and combination of references that make up the outstanding rejections fail to establish a prima facie case of obviousness by neither teaching nor suggesting to a person having ordinary skill in the art the subject conjugating agents or their suitability for nucleic acid delivery to a cell.

Accordingly, the obviousness rejection under 35 U.S.C. §103(a) with regard to claims 1-7, 9, 10, 13-18, 20, 21, and 24 should be REVERSED. Similarly, the obviousness rejection under 35 U.S.C. §103(a) with regard to claims 15 and 16 should likewise be REVERSED. Also, the obviousness rejection under 35 U.S.C. §103(a) with regard to claims 11, 12, 15 and 16 should be REVERSED.

Dated: June 6, 2008

Respectfully submitted,

By: /Avery N. Goldstein, Ph.D./
Avery N. Goldstein, Ph.D.
Registration No. 39,204
Gifford, Krass, Groh, Sprinkle,
Anderson & Citkowski, P.C.
2701 Troy Center Drive, Suite 330
P.O. Box 7021
Troy, MI 48007-7021
(248) 647-6000

Attorney for Appellant